REMARKS

The Office Action and the cited and applied reference have been carefully reviewed. No claim is allowed. Claims 93, 99, 100, 104, 106, 107, 116, 121 and 122 presently appear in this application and define patentable subject matter warranting their allowance. Reconsideration and allowance are hereby respectfully solicited.

In the event that the amendment filed April 1, 2009, cannot simply be disregarded and therefore new claim 121 added therein must be considered "unentered" with any further new claim starting with claim 122, the examiner is requested to change by examiner's amendment the numbering of new claims 121 and 122 added in the instant amendment to be claims 122 and 123, respectively, and to cancel the previously presented unentered new claim 121.

Claims 93, 99, 100, 104, 106-108, 116, 117 and 120 have been rejected under 35 U.S.C. §112, second paragraph, as being indefinite. This rejection is obviated by the amendment to claim 93.

Reconsideration and withdrawal of the rejection are therefore respectfully requested.

Claims 93, 99, 100, 104, 106-108, 116, 117 and 120 have been rejected under 35 U.S.C. §103(a) as being unpatentable over

Nakamura et al., *Infect. Immun.* 61:64-70 (1993). This rejection is respectfully traversed.

Applicants note the examiner's reference in the Office Action of July 9, 2008, to the following passage from Nakamura:

> Therefore, there is no doubt that Nakamura's factor is the same substance as the IGIF of the present invention.

Applicants however respectfully direct the examiner's attention to the disclosure in Okamura et al., *Infect. Immun.* 63(10):3966-3972 (1995), published after the earliest effective filing date of the present application, which teaches:

> In our previous studies ... 75-kDa IFN-gamma-inducing factor (IGIF) was observed in the sera of mice ... In this study, we isolated an 18- to 19-kDa IGIF from these mice and characterized it. The serum factor whose apparent molecular mass was previously found to be 75 kDa by gel filtration was shown to contain the same 18- to 19-kDa IGIF. (see page 3966 right column, lines 1-8; emphasis added)
>
> As shown in Fig.5a, an IFN-gamma-inducing activity was observed in the protein species with a molecular mass of 19 kDa ***beside*** the 75- to 80-kDa protein by molecular sieving with Superdex 75 in the presence of dithiothreitol (DTT). On the other hand, the activity was observed *only* in the molecular species of 75 to 80 kDa without DTT (21). Moreover, the molecular mass of the 75- to 80-kDa IGIF reduced to 19 kDa on 0.1% SDS-polyacrylamide gels in the presence of DTT (fig.5b). ..... Thus, IGIF in the serum sample was proved to be the same IGIF as that found in liver extract, and it was considered to be bound to another protein or to exist in an oligomeric form. (see page

3969, left column, lines 12-25; emphasis added)

As is evident from the passages cited above, the authors of the Okamura reference do not state that "the factor of 75kDa" disclosed in Nakamura is the same substance as the "IGIF of 18- to 19-kDa" disclosed in Okamura, but rather that "the factor of 75kDa" disclosed in Nakamura contains the "IGIF of 18- to 19-kDa" disclosed in Okamura. The authors clearly state that "the factor of 75kDa" disclosed in Nakamura is considered to be a substance which contains "IGIF of 18- to 19-kDa" and "another protein" bound to "IGIF of 18- to 19-kDa", or a substance which exists in an oligomeric form of "IGIF of 18- to 19-kDa". Accordingly, applicants believe that the examiner's assertion that Nakamura's factor is the same as the IGIF of the present invention is incorrect.

The examiner also seems to be of the opinion that it would have been obvious for a skilled person to obtain a monoclonal antibody against "the factor of 75 kDa" of Nakamura based on the disclosures and teachings of Nakamura. Applicants, however, disagree with the examiner on the following grounds.

As mentioned above, "the factor of 75kDa" disclosed in Nakamura is considered to be

(A) a substance which consists of "IGIF of 18- to 19-kDa" and "another protein" bound to "IGIF of 18- to 19-kDa", or

(B) a substance which exists in an oligomeric form of "IGIF of 18- to 19-kDa".

The first case (A) is considered below as follows.

If the monoclonal antibody preparation methods, known to public at the time the present invention was made, are applied to "the factor of 75 kDa" of Nakamura, various antibodies may be produced because "the factor of 75 kDa" of Nakamura contains of "IGIF of 18- to 19-kDa" and "another protein" bound to "IGIF of 18- to 19-kDa". It is clear that it would require undue experimentation to select an antibody which only specifically recognizes "IGIF of 18- to 19-kDa" from the mixtures of various antibodies which may recognize proteins other than "IGIF of 18- to 19-kDa". Please note that the "IGIF of 18- to 19-kDa" was not known at the time Nakamura was published. Therefore, how would one of ordinary skill in the art be able to select a monoclonal antibody which recognizes an unknown protein, i.e., "IGIF of 18- to 19-kDa"?

Applicants believe that the situation is the same in the second case (B). If the monoclonal antibody preparation methods, known to public at the time the present invention was made, are applied to "the factor of 75 kDa" of Nakamura, it is considered that antibodies which recognize the oligomer of "IGIF of 18- to 19-kDa" as well as "IGIF of 18- to 19-kDa" may be produced, because "the factor of 75 kDa" of Nakamura is an

oligomeric form of "IGIF of 18- to 19-kDa". It is clear that it would require undue experimentation to select an antibody which only specifically recognizes "IGIF of 18- to 19-kDa" from the mixtures of antibodies that may recognize the oligomer of "IGIF of 18- to 19-kDa" as well as the "IGIF of 18- to 19-kDa". Please again note that the "IGIF of 18- to 19-kDa" was not known at the time Nakamura was published. Again, how would one of ordinary skill in the art be able to select a monoclonal antibody which recognizes an unknown protein, i.e. "IGIF of 18- to 19-kDa"?

Nakamura states at page 68, right column, lines 18-28 that:

> The purified substance was much smaller by SDS-PAGE (50 to 55kDa)(Fig.2B) than by the molecular sieve technique (70 to 75 kDa). We could find no explanation for this. Since the molecular size was determined by molecular sieve with a rather crude sample, interaction between other molecules might have occurred. Alternatively, a small fragment might have been lost during purification procedures. The molecular shape may also have influenced the result. Since *the factor lost its activity in SDS-PAGE*, we also failed to definitely establish that the band revealed by SDS-PAGE was the factor. (see page 68, right column, lines 18-28; emphasis added)

By contrast, Okamura states at page 3968, left column, 3rd line from the bottom that:

> Highly purified IGIF was analyzed on SDS-polyacrylamide gels (Fig.3). IGIF still contained several species of protein when examined by the silver staining method. On

> the other hand, the IFN-gamma activity was recovered in the extract of SDS-polyacrylamide gels slices containing an 18- to 19-kDa peptide." (emphasis added)

The conditions of SDS-PAGE in Nakamura and Okamura are the same, including the presence of dithiothreitol (DTT). As is evident from the disclosures cited above, it is clear that the "18- to 19-kDa peptide" of Okamura revealed IFN-gamma inducing activity even after SDS-PAGE, while the factor of 70 to 75 kDa of Nakamura lost its IFN-gamma inducing activity after SDS-PAGE. If the factor of 70 to 75 kDa of Nakamura contains the "18- to 19-kDa peptide" of Okamura, then it should have revealed IFN-gamma inducing activity even after SDS-PAGE. However, this was not the case. It is therefore considered by applicants that it is uncertain whether the factor of 70 to 75 kDa of Nakamura actually contains the "18- to 19-kDa peptide" of Okamura.

Attached hereto is an executed 1.132 declaration from Dr. Haruki Okamura stating his reasons as to why the applied Nakamura reference cannot make obvious the presently claimed invention.

Reconsideration and withdrawal of the rejection are therefore respectfully requested.

In view of the above, the claims comply with 35 U.S.C. §112 and define patentable subject matter warranting their

allowance. Favorable consideration and early allowance are earnestly urged.

Respectfully submitted,

BROWDY AND NEIMARK, P.L.L.C.
Attorneys for Applicant(s)

By /ACY/
Allen C. Yun
Registration No. 37,971

ACY:pp
Telephone No.: (202) 628-5197
Facsimile No.: (202) 737-3528
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